

EDITORIAL

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Aspirin: the miracle drug?

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Abstract

Aspirin use is associated with reduction of esophageal adenocarcinoma but it is not known if it does so by preventing the development of Barrett's esophagus or by reducing neoplastic progression in patients with Barrett's esophagus. There is sparse literature to support the former assumption especially in women. This study by Jovani et al. based on Nurses' Health Study reports 27% lower risk of Barrett's esophagus among women using aspirin. The protective effect seems to increase with higher frequency and longer duration of aspirin use. This study provides evidence for lower prevalence of Barrett's esophagus in female aspirin users.

An ounce of prevention is worth a pound of cure.

—Benjamin Franklin

The medicinal use of salicylates, the key component of aspirin dates back to antiquity when salicylate rich plants, such as willow and myrtle were used for treating fever and inflammation¹. Since its introduction into the market in 1899, aspirin has veritably proven to be a miracle drug with extensive use for its analgesic and anti-inflammatory effects and subsequently for its cardioprotective effects. The chemopreventive effects of aspirin were first brought to light in 1988 by the Melbourne Colorectal Cancer study where ~50% reduction in colorectal cancer was observed users of aspirin². Subsequent studies have confirmed these findings and a recent review of over 69,224 patients in randomized controlled studies and 52,926 patients in case control studies have shown a 7–10% reduction in all cancer incidence and 9–12% reduction in mortality in 10 year users of aspirin³. The protective effect seems to be more pronounced in gastrointestinal tract (GI) cancers, such as colorectal, gastric and esophageal cancers with about 30% reduction in long-term aspirin users³. Esophageal cancer is thought to arise from stepwise progression through reflux induced inflammation to metaplasia to dysplasia to carcinoma. It is not known at what stage of this neoplastic progression does aspirin act, whether prior to development of Barrett's esophagus (BE),

or during the progression to dysplasia or esophageal adenocarcinoma (EAC) in patients with BE.

In this report, based on Nurses' Health Study, Jovani M et al.⁴ presented the prevalence of BE in women based on aspirin use. There were 667 cases of BE (defined as intestinal metaplasia of any length) among 27,881 women over 18 years of follow-up. Compared to non-regular users, women who regularly used aspirin had an adjusted odds ratio (OR) for BE ≥ 1 cm of 0.73 (95% confidence intervals (CI): 0.56, 0.96). The protective effect for BE of any length seemed to increase with frequency of use (OR 0.91 (95% CI, 0.69, 1.20) for women taking 0.5–1.5 tablets/week; 0.92 (95% CI 0.76, 1.11) for 2–5 tablets/week; and 0.71 (95% CI 0.55, 0.92) for ≥ 6 tablets/week (p -trend = 0.01) and duration of use (compared with non-regular users, OR 0.90 (95% CI 0.67, 1.20) for women who regularly used aspirin for 1–5 years, 0.84 (95% CI 0.65, 1.09) for 6–10 years, and 0.81 (95% CI 0.67, 0.97) for >10 years, p -trend = 0.03). The investigators have adjusted for various confounding variables, such as year of endoscopy, age, race, body mass index, physical activity, daily caloric intake, alcohol consumption, menopausal hormone use, smoking history, Alternative Healthy Eating Index (AHEI) score, history of frequent gastroesophageal reflux disease (GERD), use of any acid suppressive drugs, non-aspirin non-steroidal anti-inflammatory drug (NSAID) use and diabetes. This study provides strong evidence to the protective effect of aspirin against development of BE in women.

Three previous studies reported on the effect of aspirin in development of BE. In two studies, one from Kaiser

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Permanente in California and another from the Massachusetts General hospital, ~50% reduced risk of BE is seen with aspirin use^{5, 6}. It is noteworthy that women constituted about 27 and 28% of the study population respectively in these studies. In contrast, no beneficial effect was noted in a six center pooled analysis where 1474 patients with BE were compared with two control groups: 2256 population-based controls and 2018 GERD controls (fully adjusted OR = 1.00, 95% CI = 0.76–1.32)⁷. Also, there was no association between duration of prior aspirin use and risk of BE (fully adjusted OR for ≥ 5 years = 1.04, 95% CI = 0.70–1.54). These studies point to an intriguing finding: aspirin seems to be protective against development of BE in women but not so consistently in men. This raises a question whether subtle differences exist in development of BE in men and women.

A key point before recommending aspirin for chemoprevention is to define the subsets of patients at high risk for BE /EAC, patients who benefit from aspirin and patients are at high risk for side effects from aspirin. Even though upto 40 % of adult population have heartburn symptoms, only about 5.6% are estimated to have BE⁸. To address this issue, various risk prediction models have been developed based on demographic, lifestyle factors, GERD symptoms, and genetic factors⁹. However, they are not validated in independent studies nor have widespread clinical use. Also, studies are undergoing to identify patients who derive greatest benefit from aspirin use. In Seattle Barrett's Esophagus Study, strongest protective effect was seen in patients with multiple genetic abnormalities such as 17p loss of heterozygosity (LOH), DNA content abnormalities, and 9p LOH, with a 79.1% 10-year EAC incidence in non-users compared to 30% in aspirin users ($p < 0.001$)¹⁰. One factor to consider is the risk of GI bleeding and hemorrhagic stroke with aspirin which increases with age especially after 75 years. Hemorrhagic stroke is the most serious side effect of aspirin with a relative increase of 32–36% in aspirin users from a baseline rate of 0.03% per year¹¹. Aspirin use also increases GI bleeding events by 60% leading to an annual excess of 0.45 and 0.79 GI bleeding events per 1000 women and men aged 50–54 years, respectively¹².

All factors considered, aspirin seems to have a net beneficial effect. For average-risk individuals aged 50–65 years taking aspirin for 10 years, there would be a relative reduction of between 7% (women) and 9% (men) in the number of cancer, myocardial infarction or stroke events over a 15-year period and an overall 4% relative reduction in all deaths over a 20-year period¹³. However, Jovani M et al.⁴ does not report on the complications of aspirin in this cohort that would be helpful in making an informed

decision about the net beneficial effect of aspirin. As we stand at the crossroads of population health and precision medicine, it is essential to identify the population with greatest benefit from aspirin and tailor the recommendation to each individual patient depending on risk versus benefit profile.

Competing interests

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